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Autonomic Dysfunction and Blood Pressure in Glaucoma Patients: The Lifelines Cohort Study

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Purpose. We investigated relationship of glaucoma with measurements related to autonomic dysfunction, including heart rate variability (HRV) and blood pressure (BP).

Methods. Glaucoma was defined using a questionnaire-based algorithm for 86,841 LifeLines Cohort Study participants. Baseline HRV (root mean square of successive differences [RMSSD]) was calculated from resting electrocardiograms; systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP) were oscillometric-based measurements. We used a generalized linear mixed model, adjusted for age, age square, sex, body mass index, and familial relationships to assess the relationship of baseline HRV and BP (continuous and quartiles), hypertension, and antihypertensive medication with glaucoma at follow up (median, 3.8 years).

Results. The odds ratio (OR) of glaucoma was 0.95 (95% confidence interval [CI], 0.92–0.99) per unit increase in log-transformed RMSSD (in ms), indicating that autonomous dysfunction (low HRV) is associated with a higher risk of glaucoma. Per 10-mm Hg increase in BP, we found ORs of 1.03 (95% CI, 1.01–1.05; $P = 0.015$) for SBP, 1.01 (95% CI, 0.97–1.05; $P = 0.55$) for DBP, 1.03 (95% CI, 1.00–1.06; $P = 0.083$) for MAP, and 1.04 (95% CI, 1.01–1.07; $P = 0.006$) for PP. The OR for the lowest versus highest RMSSD quartile was 1.15 (95% CI, 1.05–1.27; $P = 0.003$). The ORs for the highest versus second quartile were 1.09 (95% CI, 0.99–1.19; $P = 0.091$) for SBP and 1.13 (95% CI, 1.02–1.24; $P = 0.015$) for PP. Glaucoma was more common among hypertensives (OR, 1.25; 95% CI, 1.16–1.35; $P < 0.001$); among those using angiotensin-converting enzyme (ACE) inhibitors (OR, 1.35; 95% CI, 1.18–1.55; $P < 0.001$); and among those using calcium-channel blockers (OR, 1.19; 95% CI, 1.01–1.40; $P = 0.039$).

Conclusions. Low HRV, high SBP, high PP, and hypertension were associated with glaucoma. Longitudinal studies may elucidate if autonomic dysregulation and high BP also predict glaucoma incidence.

Keywords: glaucoma, blood pressure, autonomic dysfunction, heart rate variability, hypertension, antihypertensive medication

Glaucoma is a group of complex ocular diseases accompanied by progressive damage to the optic nerve. Primary open-angle glaucoma (POAG) is the most common subtype in the Western world and Africa. Mechanical,[1,2] vascular,[3,4] genetic,[5–7] and, recently, autonomic nervous function[8] theories have been proposed to explain the mechanisms behind glaucoma. The mechanical theory refers to axonal damage of the optic nerve that is directly related to an elevated intraocular pressure (IOP), the most important risk factor for glaucoma, or possibly to an elevated pressure difference across the lamina cribrosa (IOP vs. intracranial pressure). The vascular theory proposes ischemia due to insufficient blood supply to the optic nerve head as a possible mechanism for optic nerve damage.[9] This has been linked to autonomic dysfunction, hypertension (HTN), and low blood pressure (BP). Current results are conflicting and, partially due to that, controversial.

By evaluating 24-hour BP measurements, prior studies suggest that nocturnal hypotension may be a contributing factor for anterior ischemic optic neuropathy and glaucoma.[10,11] However, abnormalities in ocular blood flow occur at both high[12,13] and low[14] BP in glaucoma, yielding a J- or U-shaped[15] relationship between BP and glaucoma. This apparent controversy has led to a new hypothesis, the involvement of autonomic nervous dysfunction. Studies speculate that autonomic dysfunction affects the susceptibility of the optic nerve to BP changes and is most prominent in normal-tension glaucoma (NTG), a glaucoma subtype where the most important risk factor, an elevated IOP, is lacking.[16,17] Autonomic dysfunction involvement in glaucoma pathogenesis is further supported by a cold provocation test, where glaucomatous individuals had greater sympathetic innervation.[17]

Compared to normal subjects, glaucoma patients exhibit blood flow abnormalities in vessels of the optic nerve head,[18] retina,[18] retrobulbar tissue,[19] and choroid.[18,20,21] With limited information regarding autonomic dysfunction involvement, several researchers proposed that ocular vessel disturbances are linked to plasma levels of endothelin-1,[22] systemic blood pressure,[23,24] and vasospasm.[25] Autonomic function reflects the effect of parasympathetic nervous system activity on the heart. Autoregulation is a related mechanism found in the nervous system that aims to maintain a stable blood flow despite changes in blood pressure, including changes in intraocular pressure.[16,19]

There is a paucity of reports investigating the role of autonomic dysfunction in glaucoma. Dysfunctional autonomic control was reported to lead to an unstable blood supply, related to a reduced perfusion pressure in glaucomatous eyes.[17,26,27] In fact, a low heart rate variability (HRV) was associated with a faster rate of central visual field loss in glaucoma.[28] HRV is a commonly used proxy measurement for autonomic modulation of the heart.[29]

Regarding glaucomatous damage and systemic BP, there are conflicting reports. The Rotterdam[30] and Beaver Dam[31] eye studies reported a higher risk of POAG with high BP, whereas the Barbados Eye Study[32] has reported the opposite. Alternatively, two US studies found a U-shaped relationship, suggesting that those with either low or high BP may be at greater risk for glaucoma.[12,15]

In this study, we explored associations of HRV and BP with glaucoma in the LifeLines Cohort Study, which involves a large cohort from the Northern Netherlands that is representative of the general population. We also studied the role of antihypertensive drugs in the relationship between glaucoma and BP. We hypothesized that participants with low HRV values, as well as those with high and low BP measurements, have higher odds of glaucoma.

Methods

Ethical Approval

The LifeLines data collection was approved by the medical ethics committee of the University Medical Center Groningen. Written informed consent was obtained from all participants, and the data collection was conducted in accordance with the tenets of the Declaration of Helsinki.

Study Design and Sample

We used phenotypic data from the LifeLines Cohort Study and Biobank, a multidisciplinary prospective population-based cohort study of the Northern Netherlands. The LifeLines cohort employs a broad range of investigative procedures to assess the sociodemographic, biomedical, physical, behavioral, and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. LifeLines participants were asked to invite their family members (i.e., partners, parents, and children), resulting in the formation of a three-generation family study. The current study included 17,379 families, with an average family size of 3.32, and 29,082 singletons (i.e., no family members included). A questionnaire on diagnosis and treatment of eye conditions, which included the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25),[33] was administered to all participants (n = 110,759) 18 years of age and older during the first follow-up visit between 2014 and 2017, after a median period of 3.8 years after baseline. Further details on design and data collection approaches used by LifeLines are described elsewhere.[34,35]

Measurement and Definition of Glaucoma

We used a previously described algorithm for defining glaucoma in LifeLines,[36] which was based on self-report of glaucoma diagnosis and treatment in combination with the NEI-VFQ-25[33] (for details, see Neustaeter et al.[36]). In short, this algorithm classifies participants as *definite*, *probable*, or *possible* glaucoma cases, or as healthy. Definite glaucoma cases were those who reported incisional surgery for glaucoma. These cases were also used to define a glaucoma-specific complaints pattern within the NEI-VFQ-25. Probable cases were those who self-reported glaucoma (including the use of IOP-lowering medication and a history of glaucoma laser treatment) together with glaucoma-specific complaints above a certain threshold. Possible cases were those who either self-reported glaucoma or had glaucoma-specific complaints. As such, the algorithm includes both participants who were aware (definite, probable, and possible glaucoma by self-report) and unaware (possible glaucoma by complaint) of their disease status. The algorithm was applied to participants in the first follow-up visit with available eye questionnaire data. In this study, unless specified otherwise, the term "glaucoma" refers to the definite, probable, and possible cases combined. Aiming for primary glaucoma, the proxy excluded participants with self-reported macular degeneration or (laser) surgery for diabetes or retinal detachment. The questionnaire did not allow for discrimination between open-angle and narrow-angle glaucoma. Based on the prevalence ratio of open-angle and narrow-angle glaucoma in the Western world, however, the majority of cases will have open-angle glaucoma.[37,38]

Predictor Variables and Covariates

Predictor variables were measured during the baseline visit from LifeLines. HRV was represented as the log of the root mean square of successive differences (RMSSD), measured in milliseconds, which quantifies normal beat-to-beat variance in heart rate and is used to estimate the vagally mediated modulation of the heart.[39] RMSSD was calculated with a 10-second resting electrocardiogram (ECG) reading (for details, see Tegegne et al.[40] and Munoz et al.[41]). We previously demonstrated the validity of RMSSD based on an ultra-short (10-second) ECG recording as a measure of HRV by comparing it to the current gold standard recording of 4 to 5 minutes.[41,42] For BP, 10 consecutive BP measurements were obtained in a supine position using an automated oscillometric method (Dinamap PRO 100V2; GE Healthcare, Chicago, IL, USA); the last three measurements were averaged to yield systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) values. MAP was provided by the device; pulse pressure (PP) was calculated as PP = SBP – DBP.[43]

High BP was defined as SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg, and HTN as high BP and/or use of antihypertensive medication. The generic names and Anatomical Therapeutic Chemical (ATC) codes of all common antihypertensive medications were obtained; angiotensin-converting enzyme (ACE) inhibitors are assigned ATC code C09A, calcium-channel blockers ATC code C08, diuretics ATC code

Table 1. Population Characteristics and Distribution of HRV and BP Data Stratified by Glaucoma Status

Variables	All Cases (n = 3838)	Possible Cases Excluded (n = 450)	Controls (n = 83,003)
Age (y), mean (SD)	53.4 (12.7)	58.4 (12.1)	46.1 (12.6)
Sex (females), n (%)	2461 (64.1)	268 (59.6)	48,921 (58.9)
BMI (kg/m^2), median (IQR)	26.2 (23.8–29.1)	26.1 (23.9-–29.3)	25.4 (23.1–28.1)
HRV (lnRMSSD, ms), median (IQR)	3.1 (2.6–3.5)	3.0 (2.6-3.5)	3.3 (2.8-3.7)
SBP (mm Hg), median (IQR)	127 (117–140)	130 (120–142)	124 (115–135)
DBP (mm Hg), median (IQR)	74 (68–81)	74 (68–82)	73 (67–80)
MAP (mm Hg), median (IQR)	94 (88–102)	95 (89-–103)	92 (87–99)
PP (mm Hg), median (IQR)	53 (45–62)	54 (46–64.3)	50 (44–58)
High BP, n (%)	1018 (26.6)	135 (30)	15,410 (18.6)
HTN, n (%)	1568 (40.9)	215 (47.8)	21,609 (26.0)

High BP was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg and HTN as high BP and/or use of antihypertensive medication. lnRMSSD, logarithm of root mean square of successive differences between normal-to-normal intervals.

C03, and beta-antagonists ATC code C07. The effects of (1) any antihypertensive medication use, (2) number of antihypertensive medications, and (3) different antihypertensive medication classes were investigated. Based on evidence of associations with glaucoma, data analyses were adjusted for the effects of age, age square, sex, and body mass index (BMI).[37,44–46] BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2), from the baseline assessment.

Data Analysis

Our analyses estimated the association of HRV and BP-related measurements at baseline with glaucoma at follow-up, with a median interval of 3.8 years (interquartile range [IQR], 3.1–4.5). We separately investigated the association of HTN and antihypertensive medication use with glaucoma. To test associations, we applied generalized linear mixed models (GLMMs), in order to adjust for family membership.

First, we combined the three glaucoma classes. Next, we performed the analyses after excluding possible glaucoma cases, as there is less certainty in this category. Finally, we performed the analyses separately for those who were aware of having glaucoma and for those who were not aware (for definitions, see the Measurement and Definition of Glaucoma section). The rationale behind this separation is that clinical glaucoma cases (aware) differ from glaucoma cases captured during glaucoma screening (unaware); in the latter group, NTG dominates,[47,48] and, as such, unawareness may serve as a surrogate for NTG in the current study. We used GLMM to test the association of HRV, BP-related measurements, HTN, and antihypertensive medications with glaucoma. A separate model was built for each predictor, except for the classes of antihypertensive medications, which were put together in one model. Measurements were analyzed as continuous traits and as quartiles to accommodate potential nonlinear effects. In all models, age, age square, sex, and BMI were used as covariates. In models investigating effects of BP variables, we additionally investigated interaction by antihypertensive medication status followed by a stratified analysis. In models investigating effects of the various antihypertensive medication classes, we additionally adjusted for the different BP measurements.

In the mixed models, we assumed individuals to be level-1 observation units clustered by family membership (level-2). Fitting the logit link function, the odds of glaucoma for individual i, (i = 1, 2, 3, …, n) in a family j (j = 1, 2, 3, …, m) was estimated as follows:

$$\log\left(p_{ij}/1-p_{ij}\right) = \mu + \beta_i X_i + a_j + e_{ij},$$
$$\text{with } a_j \sim \mathrm{N}\left(0, \sigma_j^2\right) \text{ and } e_{ij} \sim \mathrm{N}\left(0, \sigma_e^2\right)$$

where, p_{ij} is the probability of glaucoma status, μ is the overall mean, β_i represents the fixed effects, X_i represents the prediction variables and covariates (age, age square, sex, BMI), a is the random effect due to the family relationship, and e is random error. Data reorganization and cleaning and descriptive analyses were performed in R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics 23 (IBM, Armonk, NY, USA). GLMM analyses were executed in ASReml 4.1 (VSNi, Hempstead, UK). Statistical significance was set at a P value of 0.05 or less.

Results

Of the 110,759 participants invited for the follow-up assessment, 88,584 (80%) had eye-related data. After excluding 1,743 participants who underwent laser treatment or surgery for diabetes or retinal detachment or who had age-related macular degeneration (see Methods section), the total number of study participants included in the analyses was 86,841. There were 102 (0.11%) definite glaucoma cases, 348 (0.40%) probable cases, and 3388 (3.90%) possible cases. Of the possible cases, 1585 (1.82%) were possible by self-report, and 1803 (2.07%) were possible by complaint. Table 1 shows the characteristics of the study population and the distribution of HRV and BP data between cases and controls. We confirmed the well-known relationship between glaucoma and age; that is, we found a significant positive relationship between glaucoma and age across all age groups compared to individuals 55 years old (Supplementary Table S1).

All Glaucoma Cases Combined

We found a negative relationship between glaucoma and baseline HRV, represented by RMSSD. The odds ratio (OR) of glaucoma was 0.95 (95% confidence interval [CI], 0.92–0.99; P = 0.005) per unit increase in log-transformed RMSSD (with RMSSD expressed in ms), which means that autonomous dysfunction (low HRV) is associated with a higher risk of glaucoma (Fig., part A). Alternatively, most BP-related measurements, including SBP, PP, high BP, HTN, and the use of antihypertensive medication, showed a significant

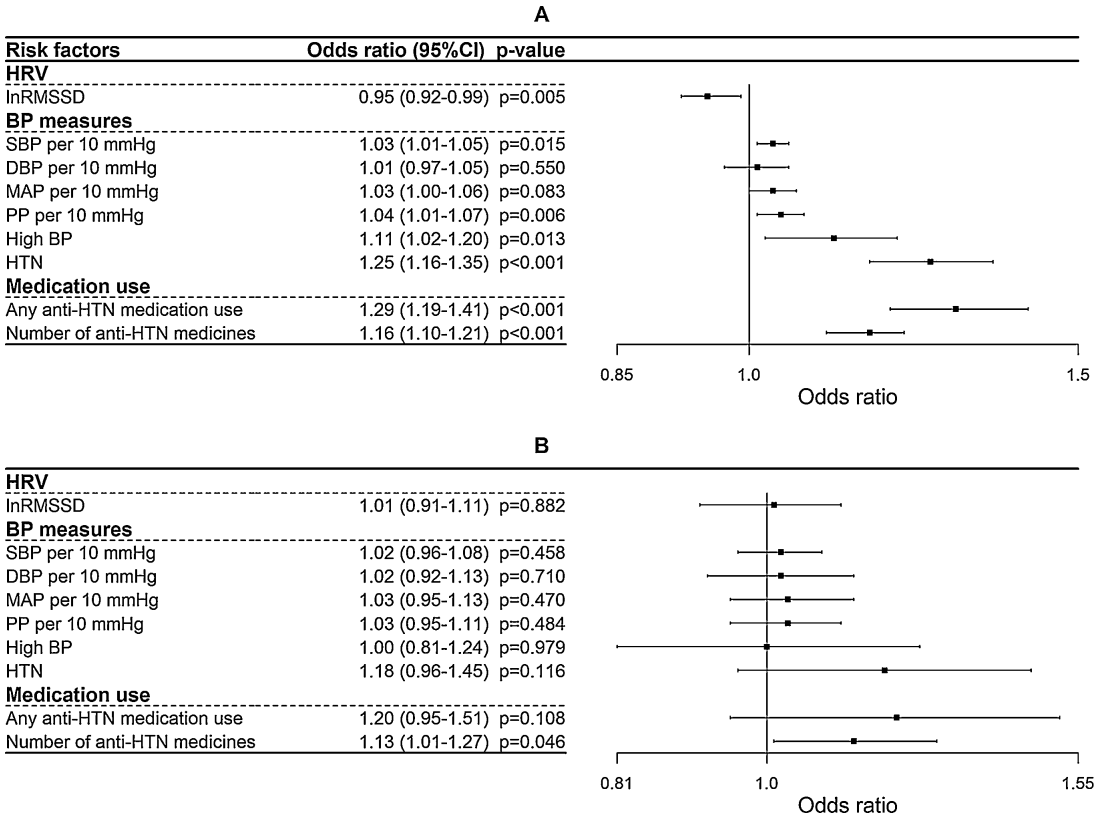

Figure. Association of glaucoma with HRV and BP-related measurements before (A) and after (B) excluding possible glaucoma cases. High BP was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg and HTN as high BP and/or use of antihypertensive medication. The GLMM was adjusted for age, age square, sex, and BMI. The number of anti-HTN medications (combinations) was modeled as a continuous variable.

Table 2. Association of Glaucoma with Antihypertensive Medication Use

	All Cases			Possible Cases Excluded		
Antihypertensive Medication Class	**Glaucoma Cases/Controls**	**OR (95% CI)**	***P***	**Glaucoma Cases/Controls**	**OR (95% CI)**	***P***
Beta-antagonists	403/4613	1.06 (0.94–1.19)	0.319	60/4613	1.06 (0.78–1.42)	0.695
Diuretics	292/2858	1.09 (0.95–1.25)	0.229	41/2858	0.99 (0.69–1.42)	0.982
ACE inhibitors	299/2908	**1.35 (1.18–1.55)**	**<0.001**	50/2908	**1.48 (1.07–2.06)**	**0.017**
Angiotensin II blockers	187/1943	1.16 (0.98–1.37)	0.080	22/1943	0.86 (0.54–1.35)	0.515
Calcium-channel blockers	191/1734	**1.19 (1.01–1.40)**	**0.039**	30/1734	1.16 (0.78–1.73)	0.443
Other medication use	25/220	1.29 (0.84–2.00)	0.243	5/220	1.97 (0.79–4.92)	0.142

Models were adjusted for age, age square, sex, and BMI. Other medications included renin inhibitors, alpha-/beta-blockers, alpha blockers, alpha agonists, antiadrenergics, serotonin antagonists, potassium channel enhancers, and smooth muscle relaxants. Values with statistical significance are shown in bold.

positive association with glaucoma; see part A of the Figure for the results of the continuous trait analysis. After stratifying by type of medication, only ACE inhibitors and calcium-channel blockers were statistically significant (Table 2), showing a harmful effect. These medication effects did not change when adjusting for BP measurements (Supplementary Table S2).

When analyzed in quartiles (Table 3), participants in the lowest quartile of log-transformed RMSSD demonstrated a higher odds ratio for glaucoma (OR, 1.15; $P = 0.003$). For BP-related measurements, PP was significantly associated with glaucoma, as participants in the highest quartile of PP were 1.13 times more likely to have glaucoma ($P = 0.015$) compared to those in the second quartile.

Neither continuous nor categorical BP analyses showed significant interactions by antihypertensive medication status (data not shown), but, when stratified by antihypertensive medication status, more clearly positive associations between BP and glaucoma in those not taking antihypertensive medication was observed (Supplementary Table S3).

Table 4 shows the effect of the various risk factors for participants who were aware of their glaucoma status (definite, probable, and possible by self report, $n = 2035$ cases) versus those who were not (possible by complaint, $n = 1803$; a NTG surrogate, as described in the Methods section). The risk of high BP was observed only among participants who were aware of their glaucoma status. In contrast, HRV was significantly associated with glaucoma in both groups,

Table 3. Odds Ratios of Glaucoma for Different Categories of HRV and BP-Related Measurements (Quartiles)

	All Cases			Possible Cases Excluded		
Predictor	**Glaucoma Cases/Controls**	**OR (95% CI)**	***P***	**Glaucoma Cases/Controls**	**OR (95% CI)**	***P***
HRV (lnRMSSD)						
≤2.85	1272/19,905	**1.15 (1.05–1.27)**	**0.003**	159/19,905	1.07 (0.82–1.41)	0.610
2.86–3.30	946/19,968	1.05 (0.95–1.16)	0.312	113/19,968	1.09 (0.82–1.45)	0.561
3.31–3.77	796/20,124	1.03 (0.93–1.14)	0.603	91/20,124	1.14 (0.85–1.54)	0.384
≥3.78	645/20,267	Reference	—	62/20,267	Reference	—
SBP (mm Hg)						
≤115	805/21,907	0.99 (0.89–1.09)	0.818	70/21,907	0.84 (0.61–1.15)	0.284
116–124	826/20,347	Reference	—	94/20,347	Reference	—
125–135	965/21,019	1.02 (0.93–1.12)	0.689	131/21,019	1.12 (0.85–1.46)	0.417
≥136	1238/19,696	1.09 (0.99–1.19)	0.091	155/19,696	0.91 (0.70–1.20)	0.515
DBP (mm Hg)						
≤67	879/21,456	0.98 (0.89–1.08)	0.450	96/21,456	0.93 (0.71–1.21)	0.575
68–73	1027/22,166	Reference	—	128/22,166	Reference	—
74–80	916/20,337	**0.91 (0.83–1.00)**	**0.048**	97/20,337	**0.74 (0.57–0.97)**	**0.03**
≥81	1012/19,010	1.01 (0.92–1.11)	0.810	129/19,010	0.95 (0.74–1.22)	0.681
MAP (mm Hg)						
≤87	719/21,191	0.97 (0.88–1.07)	0.660	55/21,191	**0.68 (0.50–0.91)**	**0.008**
88–92	774/21,863	Reference	—	92/21,863	Reference	—
93–99	949/20,023	0.97 (0.88–1.07)	0.528	119/20,023	0.81 (0.62–1.06)	0.118
≥100	1391/19,885	1.01 (0.92–1.11)	0.849	184/19,885	**0.78 (0.61–1.00)**	**0.05**
PP (mm Hg)						
≤44	842/22,795	1.00 (0.91–1.11)	0.968	84/22,795	0.90 (0.66–1.21)	0.483
45–50	757/18,987	Reference	—	88/18,987	Reference	—
51–58	890/20,619	1.00 (0.91–1.11)	0.936	108/20,619	0.97 (0.73–1.29)	0.841
≥59	1315/20,568	**1.13 (1.02–1.24)**	**0.015**	170/20,568	0.94 (0.72–1.24)	0.674

The GLMM was adjusted for age, age square, sex, and BMI. Values with statistical significance are shown in bold.

Table 4. Association of Glaucoma with HRV, BP-Related Measurements, and Antihypertensive Medication Use for Cases Who Were Aware of Their Glaucoma Status Versus Those Who Were Unaware

	Glaucoma Cases Aware of Their Glaucoma Status/Controls (2035/83,003)		Glaucoma Cases Unaware of Their Glaucoma Status/Controls (1803/83,003)	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
HRV				
lnRMSSD	0.95 (0.91–0.99)	0.045	0.95 (0.90–1.00)	0.044
BP measurements, per 10 mm Hg				
SBP	1.08 (1.04–1.11)	<0.001	0.98 (0.95–1.01)	0.173
DBP	1.07 (1.02–1.12)	0.008	0.95 (0.90–1.01)	0.078
MAP	1.10 (1.05–1.14)	<0.001	0.96 (0.92–1.01)	0.107
PP	1.09 (1.05–1.13)	<0.001	0.99 (0.95–1.03)	0.681
High BP	1.21 (1.09–1.35)	<0.001	0.97 (0.86–1.10)	0.659
HTN	1.33 (1.20–1.47)	<0.001	1.16 (1.04–1.29)	0.008
Medication use				
Any anti-HTN medication use	1.25 (1.11–1.40)	<0.001	1.35 (1.19–1.53)	<0.001
Number of anti–HTN medications	1.13 (1.06–1.21)	<0.001	1.18 (1.10–1.26)	<0.001

The GLMM was adjusted for age, age square, sex, and BMI. The number of anti-HTN medications (combinations) was modeled as a continuous variable.

as was the effect of antihypertensive medication. A similar pattern was seen in the corresponding quartile analysis (Table 5).

After Exclusion of Possible Glaucoma Cases

We repeated association testing for HRV, BP, high BP, HTN, and medication use with glaucoma status after excluding the possible cases. Although the direction of the effects remained unchanged, excluding 88% (n = 3388 possible cases) of the 3838 total glaucoma cases resulted in low power to detect significant differences between cases and controls (Fig., part B; Table 3).

Discussion

Our findings show that HRV has a negative relationship with glaucoma, whereas BP-related measurements, including HTN, high BP, and antihypertensive medication use (especially ACE inhibitors and calcium-channel blockers), have a positive association with glaucoma prevalence. Our findings support previous work where lower HRV was

Table 5. Association of Glaucoma with HRV and BP-Related Measurements for Cases Who Were Aware of Their Glaucoma Status Versus Those Who Were Unaware (Quartiles)

	Glaucoma Cases Aware of Their Glaucoma Status/Controls (2035/83,003)		Glaucoma Cases Unaware of Their Glaucoma Status/Controls (1803/83,003)	
Variables (Quartile)	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
HRV, LnRMSSD (ms)				
≤2.85	**1.14 (1.00–1.29)**	**0.043**	**1.16 (1.01–1.33)**	**0.031**
2.86–3.30	1.02 (0.89–1.17)	0.749	1.09 (0.94–1.25)	0.250
3.31–3.77	1.02 (0.88–1.17)	0.787	1.04 (0.90–1.20)	0.610
≥3.78	Reference	—	Reference	—
BP, mm Hg				
SBP				
≤115	0.92 (0.79–1.06)	0.262	1.05 (0.91–1.20)	0.515
116–124	Reference	—	Reference	—
125–135	1.08 (0.94–1.23)	0.258	0.96 (0.84–1.11)	0.596
≥136	**1.21 (1.06–1.38)**	**0.003**	0.94 (0.82–1.08)	0.412
DBP				
≤67	0.92 (0.80–1.05)	0.2	1.04 (0.91–1.19)	0.548
68–73	Reference	—	Reference	—
74–80	0.91 (0.80–1.03)	0.149	0.91 (0.80–1.04)	0.167
≥81	1.07 (0.94–1.20)	0.3	0.93 (0.82–1.07)	0.327
MAP				
≤87	**0.86 (0.75–0.99)**	**0.043**	1.07 (0.93–1.22)	0.342
88–92	Reference	—	Reference	—
93–99	0.93 (0.81–1.06)	0.271	1.02 (0.89–1.17)	0.779
≥100	1.11 (0.98–1.26)	0.093	0.87 (0.76–1.00)	0.058
PP				
≤44	0.90 (0.78–1.04)	0.149	1.11 (0.97–1.28)	0.138
45–50	Reference	—	Reference	—
51–58	1.03 (0.89–1.18)	0.667	0.98 (0.85–1.14)	0.810
≥59	**1.18 (1.03–1.34)**	**0.011**	1.07 (0.93–1.24)	0.317

The GLMM was adjusted for age, age square, sex, and BMI. Values with statistical significance are shown in bold.

associated with higher prevalence and faster rates of central visual field loss in NTG.[28,49] Our findings regarding HRV also agree with reports proposing that autonomic dysfunction contributes to the pathophysiology of glaucoma. For example, choroidal parasympathetic innervation increases choroidal blood flow, whereas sympathetic innervation has the opposite effect. Given that the choroid contributes to the prelaminar blood supply of the optic nerve head,[50] and predominant sympathetic innervation over-constricts microvessels nourishing the optic nerve head, the inability to maintain a constant blood supply may promote occurrence of the disease.[27,51–53] The results of our NTG surrogate subanalysis also strengthen previous evidence that autonomic dysregulation plays a role in glaucoma.[28,49] HRV was at least as significant in the unaware group as in the aware group at a similar sample size.

Our results showed an increasing trend of glaucoma at high BP. These findings support previous population-based cross-sectional studies where increases in BP are associated with increased odds of glaucoma. This was found in the Rotterdam Eye Study,[54] the Beaver Dam Eye Study,[31] the Blue Mountain Eye Study,[13] and the Egna–Neumarkt Eye Study.[55] Our findings also agree with the Los Angeles Latino Eye Study with respect to SBP and MAP, but not for DBP (see next paragraph). Our findings contradict the Barbados Eye Study in terms of SBP; that study reported an OR for glaucoma of 0.91 (95% CI, 0.84–1.0) per 10-mm Hg increase in SBP.[32] Our findings are in line with a general practitioner study from the United Kingdom, where glaucoma was more common among hypertensive individuals (OR, 1.29; 95% CI, 1.23–1.36; $P < 0.001$).[56] Furthermore, a meta-analysis of 27 observational studies reported an overall relative risk of 1.16 (95% CI, 1.05–1.28; $P < 0.05$) of glaucoma among hypertensive individuals.[57]

In the current study, we did not find a J- or U-shaped relationship (higher risk at both extremes) between glaucoma and BP. In the National Health and Nutrition Examination Survey (NHANES) cross-sectional study, Kim et al.[15] reported a U-shaped relationship between SBP and glaucoma among individuals without antihypertensive medications, but not among those taking medication. However, this finding contradicts the notion that overtreatment of HTN (excessive BP lowering due to antihypertensive medication) may reduce ocular blood flow, with ischemia as a consequence.[9] Similarly, in the Los Angeles Latino Eye Study (LALES), the U-shaped relationship came from high SBP (SBP > 170 mm Hg; OR, 2.1; 95% CI, 1.1–4.0) and low DBP (DBP ≤ 60; OR, 1.9; 95% CI, 1.1–3.0).[12] Possible explanations for the apparent discrepancy between NHANES and LALES and our study are differences in ethnicity, model building, and glaucoma definition. The reported proportion of Caucasian ethnicity was 76% and 0% in NHANES[15] and LALES,[12] respectively, compared to 98.3% in our study. Furthermore, the final statistical model in LALES[12] was corrected for the effects of IOP, a history of high BP, and use of antihypertensive medication, whereas the model used in

NHANES was adjusted for antihypertensive medication but not for IOP.

We did not adjust for IOP (data not available), and variables related to BP were studied one at a time. Stratification of our BP analyses by antihypertensive medication status clearly confirmed the positive association between BP and glaucoma in those not taking antihypertensive medication, but there was no indication of a J- or U-shaped relationship. Glaucoma was defined based on fundus photographs only in NHANES and on a combination of fundus photographs and a visual field test in LALES, whereas our glaucoma definition was based on a questionnaire-based algorithm. Cases detected with fundus photography and visual field testing in a population-based setting tend to have a normal to nearly normal IOP; that is, NTG is frequently found. The role of low blood pressure has previously been linked to NTG.[58]

Self-reported glaucoma is one of the features of the glaucoma classification algorithm in LifeLines; thus, glaucoma with elevated intraocular pressure might be more frequent in this sample. This may explain the nonsignificance of hypotension in our primary analysis. Interestingly, the subgroup of participants who were unaware of their disease status, our NTG surrogate, did not show a positive relationship with any of the BP-related traits but did show an association with antihypertensive medication, where overtreatment may play a role. The fact that high BP was only significant in the aware group suggests that either high BP is mainly associated with glaucoma with elevated pressures or that ascertainment bias plays a role (those with high BP are more likely to have their glaucoma detected). A possible reason why high BP relates to glaucoma could be the association between blood pressure and IOP.[59]

Suggested mechanisms that explain how high BP affects the optic nerve head, with ischemia as a consequence, include blood vessel size that determines blood flow velocity to the optic nerve head.[9,60] The significant relationship between high PP and glaucoma may reflect the role of vascular aging; thickening and deposition of collagen in the arterial walls alters normal blood flow to vital organs, including the eye.[61]

There are controversies among studies investigating the effects of antihypertensive medication on glaucoma. Our study demonstrated that glaucoma is more prevalent in hypertensive individuals, and the use of each additional antihypertensive medication was associated with a 16% increase in the odds of glaucoma. However, when we stratified by class of antihypertensive medications, only ACE inhibitors and calcium-channel blockers showed statistically significant relationships. These effects were independent of BP, per se, as shown by additionally adjusting for BP measurements. Our findings agree with previous population-based work in the United Kingdom, where ACE inhibitors and calcium-channel blocker medication users were more often diagnosed with glaucoma (OR, 1.16; 95% CI, 1.09–1.24; OR, 1.34; 95% CI, 1.24–1.44, respectively).[56] Similarly, a 6.5-year follow-up study (Rotterdam Study; median age 71 years; predominantly Caucasian descent)[62] showed an increased glaucoma incidence (1.8-fold; 95% CI, 1.04–3.2; $P = 0.037$) among individuals taking calcium-channel blockers. They did not find any effect (neither protective nor harmful) for ACE inhibitors. ACE inhibitors are effective in controlling BP and are typically used in patients with renal hypertension.[63] Thus, the strong association of ACE inhibitors with glaucoma as observed by us may indicate a role for the kidney in glaucoma, which is worth exploring in future studies.

In the Barbados Eye Studies[32] (mean age 56.9 years; >90% African descent) with 9-year follow-up, antihypertensive medication did not show a relationship with glaucoma risk. However, the effects of separate antihypertensive medication classes were not investigated, as the effect of antihypertensive medication was simply modeled as "yes" or "no." In a recent clinical study by Zheng et al.,[64] calcium-channel blocker usage was associated with a 26% increased risk of glaucoma ($P < 0.05$), although no dose–response relationship was observed. In the Thessaloniki Eye Study, all classes of antihypertensive medications were associated with more glaucomatous damage among subjects with DBP < 90 mm Hg.[65] In the same cohort, when compared to untreated normal DBP (< 90 mm Hg), a significantly larger cup area and cup-to-disc ratio were observed in those with the same DBP secondary to antihypertensive medication.[66] One explanation could be that excessive BP lowering in response to antihypertensive medication use, in eyes with compromised vessels due to chronic high BP, may result in lower perfusion of blood to retinal ganglion cells, with ischemia as a consequence.[67,68]

In contrast, a large prescription-based study from Denmark[69] reported that, except for vasodilators, all classes of antihypertensive medications were significantly associated with a later onset of glaucoma. Because the vascular component is a suggested mechanism involved in glaucoma development and progression, it seems logical to assume that all antihypertensive medications could also prevent the occurrence of glaucoma. The authors defined glaucoma by the use of any glaucoma medication; given that glaucoma medications are also prescribed for ocular hypertension, their outcome measure could be a mixture of glaucoma and ocular hypertension. This suspicion is supported by the overall glaucoma prevalence estimate of 4.3% (1996–2012) among people 40 to 95 years old that was reported in a Danish paper,[69] which is higher than the registry-based (i.e., based on the International Classification of Diseases, Tenth Revision) definition of glaucoma (1.4–1.9%)[70] and also higher than the European prevalence estimate of 2.93% (95% CI) for 2013.[37] An alternative explanation could be that, in the Danish healthcare system, high BP is detected and treated relatively early, resulting in less damage to the blood vessels (see below). Similar to the Danish study, a recent prospective cohort study of glaucoma patients and glaucoma suspects, the Groningen Longitudinal Glaucoma Study, reported that the use of ACE inhibitors and angiotensin II receptor blockers was associated with a lower conversion rate of glaucoma suspects.[71]

Clearly, the complex association among glaucoma, high BP, and antihypertensive drugs is not yet fully understood. By merging the above-mentioned findings, a tentative hypothesis could be that some antihypertensive drug classes possess neuroprotective properties, but these effects are only visible if prescribed in a timely manner.[69,71] A high BP itself promotes glaucoma, and, if BP is treated late and/or suboptimally, antihypertensive drugs may simply reflect a history of high BP, which may, in the past, have increased risk of glaucoma development.

Our study has a number of strengths, but also some limitations. Our findings are based on a much larger sample size than most previous studies, rendering more power to precisely estimate effect sizes; however, we need to be aware of the predictive limitation of the cross-sectional design in establishing exposure–outcome relationships. Furthermore, we used GLMM to properly adjust for familial relationships

that otherwise could have inflated the significance of associations of HRV and BP with glaucoma. We used a systematic approach for defining glaucoma, but it is likely that not all *possible* glaucoma cases are truly affected, which may result in misclassification errors. Almost all study participants (98.3%) were Caucasian, so direct comparison with other multi-ethnic study results may not be possible. Therefore, the results of this study should be interpreted with these limitations taken into account.

Conclusions

In summary, using a large population-based cohort, we examined the association of HRV, BP, high BP, HTN, and antihypertensive medication use with glaucoma. Except for HRV, which showed a negative relationship, all other variables (BP, high BP, HTN, and antihypertensive medication use) showed a positive association with glaucoma. Our results indicate that, in addition to the traditional risk factors (elevated eye pressure, family history, age, and ethnicity), low HRV and high BP may play a role in glaucoma pathophysiology. Further population-based prospective studies may help to better understand the effect of BP and the role of autonomic dysregulation in predicting glaucoma. Given that the relationship of antihypertensive medication with glaucoma remains controversial even in prospective studies,[32,62] other designs such as randomized clinical trials or Mendelian randomization studies are needed to investigate which classes of antihypertensive medications truly have a causal relationship with glaucoma.[72]

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